UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,112	12/26/2001	Andre Rosowsky	48460(70157)	5913

7590 02/28/2003

Dike Bronstein Robert & Cushman
Edwards & Angell
PO Box 9169
Boston, MA 02209

EXAMINER
MCKENZIE, THOMAS C

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 02/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/890,112	Applicant(s) ROSOWSKY, ANDRE	
	Examiner Thomas McKenzie Ph.D.	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *2* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9 and 11-26* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to an election filed on 1/6/03. There are twenty-six claims pending and twenty-five under consideration. Claims 1 and 3-10 are compound claims. Claim 26 is a composition claim. Claims 11-15 are use claims. This is the first action on the merits. The application concerns some dibenazepine compounds, compositions, and uses thereof.

Election/Restrictions

2. Applicant's election with traverse of Group III in Paper No. 7 is acknowledged. The traversal is on the ground(s) that the Examiner failed to classify the different groups, that no search burden is present, and that Groups II-VII share a common core. This is not found persuasive because firstly, the present application was filed under 35 U.S.C. 371 not 35 U.S.C. 111(a) and the unity of invention standards, not US restriction practice applies. Thus, classification is not required.

Secondly, according to the MPEP §1850, "[i]f, however, an independent claim does not avoid the prior art, then the question whether there is still an inventive link between all the claims dependent on that claim needs to be carefully considered. If there is no link remaining, an objection of lack of unity (that is, arising only after assessment of the prior art) may be raised." As discussed in the original restriction requirement of paper No. 5, Applicant's claim 1 does not avoid

the prior art. Also, according to the MPEP §1850 "[w]hen the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled: (A) All alternatives have a common property or activity; and (B) (1) A common structure is present, i.e., a significant structural element is shared by all of the alternatives;". Applicants' multiple inventions lack a common structure. Thus, the issue of search burden does not apply. In point of fact, Applicant's diverse rings fall into different classes of the US Patent classification system. Thirdly, Groups II-VII include core rings ranging in size from six to eight membered. These rings may contain one or two heteroatoms selected from nitrogen, oxygen, or sulfur. This is not the required common structure. The requirement is still deemed proper and is therefore made FINAL.

3. Claim 2 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups XIII and XIV, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

4. Applicant's comments concerning the dihydro-azepines, compounds with X = nitrogen and Z = $-CH_2-CH_2-$ as well as the dihydro-diazepines, compounds with X = nitrogen and Z = $-N-CH_2-$ are noted. These would belong to Groups III and

IV respectively. To clarify the issue, Applicant's elected Group III is drawn to 5-substituted Dibenzazepines, compounds with X = nitrogen and Z = optionally substituted ethylene and optionally substituted vinyl. The Examiner regrets the lack of clarity.

5. Objection is made to and parts of claims 1 and 3-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups I, II, and IV-XV. The claimed compounds, compositions, and methods that employ them present a variable core. Formula I contains compounds drawn to the non-elected inventions and includes compounds other than X = nitrogen and Z = optionally substituted ethylene and optionally substituted vinyl.

Specification

6. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required. The Examiner suggests claim 1 including the figure and utility.

7. The disclosure is objected to because of the following informalities: in lines 25-26, page 8 and lines 5-7, page 9, Applicant states that alkyl, alkenyl, and alkynyl groups include cyclic structures. An alkyl group is the group formed by the removal of hydrogen from an alkane. It cannot be cyclic. The word "alkyl" is an art recognized term with a specific meaning. To quote Hawley "alkyl. A paraffinic hydrocarbon..." and "paraffin ...hydrocarbons characterized by a

straight or branched carbon chain". Please also see point #13. Appropriate correction of the specification is required. The Examiner suggests deleting reference to cyclic groups.

Title

8. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: adding the word "Dibenz[b,f]azepine" before the word "Compounds".

Claim Objections

9. Claims 11-18 and 22-26 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-9, and 11-16 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant repeatedly claims "optionally substituted" aryl, alkyl, *etc.* Optionally substituted by what? In lines 17-29, page 3 Applicant describes what he intends by aryl, alkyl, *etc.* but makes no mention of

what substituents are intended. In lines 20-23, page 8 Applicant provides a list of halogen substituents. Are these the only substituents included in the claims?

11. Claims 1, 5-8, and 11-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claims 1 and 5-7, in the definition of variable W, Applicant uses the limitation "having 1 to about 3 carbon atoms". This is indefinite because the word "about" fails to clearly delineate Applicant's invention. Since atoms occur only in whole units, we understand that 2.9 or 3.1 carbon atoms are not intended. However does "about 3 carbon atoms" mean 3 or could it be 4? Could Applicant intend this to mean at most 2?

The Examiner suggests removing the word "about".

12. Claims 1, 3-9, and 11-16 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the definition of R^1 and R^2 in claims 1 and 3-7 Applicant has the limitation "optionally substituted alkyl preferably,". This is indefinite for two reasons. Firstly, because of the punctuation it is unclear if "preferably" applies just to alkyl or to the list of substituents which follows. Secondly, a broad range or limitation together with a narrow range or

limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 and 3-7 recites the broad recitation halogen, hydroxyl etc, and the claim also recites "alkyl preferably" which is the narrower statement of the range/limitation.

The Examiner suggests removing the word "preferably".

13. While applicant may be his or her own lexicographer, a term in a claim may not be given a meaning repugnant to the usual meaning of that term. See *In re Hill*, 161 F.2d 367, 73 USPQ 482 (CCPA 1947). The term “alkyl”, "alkenyl", and "alkenyl" in claims 1 and 3-7 is used by the claim to mean "alkyl or cycloalkyl",

"alkenyl or cycloalkenyl" and "alkynyl or cycloalkynyl", while the accepted meaning is "alkyl", "alkenyl", and "alkenyl". An alkyl group may not be cyclic for reasons discussed above.

14. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Variables T, U, and V may be "optionally substituted nitrogen", yet in Formula III all three atoms have three required bonds. Nitrogen is a trivalent atom. In a six-membered ring it is not chemically possible for a nitrogen atom to have an external substituent.

The Examiner suggests removing "optionally substituted" concerning nitrogen.

15. Claims 19-25 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: in claims 19-21 Applicant fails to give any physical act he intends to use to treat *Toxoplasma gondii* or tuberculosis infections, just his desire to do so.

16. Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Has the word "comprising" been omitted as the fifth word in this claim?

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating patients suffering from diseases, does not reasonably provide enablement for treating patients "susceptible to a" disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. It is presumed that prevention of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted. The Examiner suggests deletion of the phrase "susceptible to a".

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*,

230 USPQ 546. As discussed above, preventing diseases requires identifying those patients who will acquire the disease before infection occurs. This would require extensive and potentially opened ended clinical research. The paragraph spanning pages 16-17 lists the diseases Applicant intend to treat. In the final two sentences there is a discussion of AIDS and cancer patients. Are these the only patients "susceptible to a" infection, or are there others? There is no working example of such a preventive procedure in man or animal in the specification. The claims rejected are drawn to clinical infective medicine and are therefore physiological in nature. The state of the art is that no general procedure is art-recognized for determining which patients generally will become infected before the fact. The artisan using Applicants invention would be a Board Certified physician in infectious diseases with an MD degree and several years of experience. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The claims broadly read on all patients, not just those undergoing immunosuppressive therapy and on the multitude of compounds embraced by Formula I.

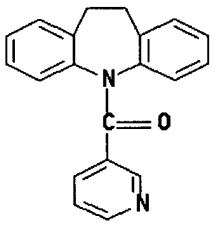
18. Claim 17 has the additional limitation, "or will be receiving immunosuppressive cancer chemotherapy". This would appear to require the artisan using Applicants' invention to possess a crystal ball.

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

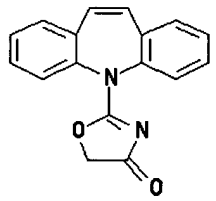
> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 5, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Mueslin (CH 372,675). The compound shown below fits formula I with Ar = 3-pyridyl, W = methylene substituted by the divalent group oxo, Z = ethylene (-CH_2-CH_2-), T = nitrogen, U = V = CH, and m = n =0,. It has Registry Number 94542-58-2 and is found in the passage spanning line 71, page 1 to line 11, page 2 of the reference.

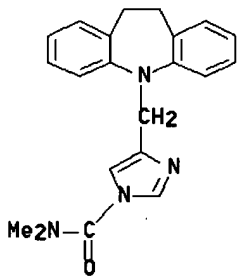


20. Claims 1, 9, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Marangos (European Journal of Pharmacology). The compound shown below

fits formula I with Ar = 2-oxazolyl, substituted in the 3-position by hydroxyl, W = a bond, Z = substituted vinyl, and m = n =0,. It has Registry Number 88265-32-1 and is found in Table 2, page 179 of the reference. It is called compound CGP-7137. Please note it is pictured below as a tautomer in its' keto form. An ED_{50} for oral dosing in an *in vivo* assay is presented. From this it is inherent that a pharmaceutical composition of CGP-7137 was prepared.



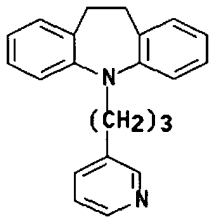
21. Claims 1, 3, 8, 9, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Kihara ('200). There are two compounds in this reference, which anticipate Applicant's claims. The compound shown below fits formula I with Ar = 4-imidazolyl substituted in the 1 position by dimethylcarboxamido, W = methylene ($-CH_2-$), Z = ethylene ($-CH_2-CH_2-$), and m = n =0. It has CAS Registry



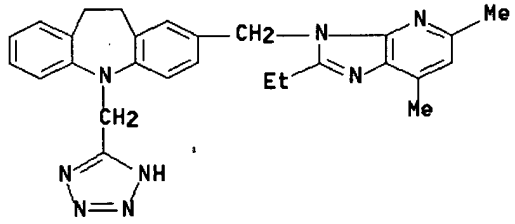
Number 121278-83-9 and is found in Table 1, column 5 of the reference. It is

compound No. 9 and its' synthesis is described in Example 5, lines 25-36, column 10. One may infer from Example 4 of the reference that the compound lacking the dimethylcarboxamido group at position 1 was an intermediate in the synthesis. Biological testing of compound 9 is taught in lines 14-50, column 13. The solution described in lines 14-15 is a composition. Thus, Applicant's claim 26 is anticipated.

22. Claims 1, 5, 8, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Andreani (European Journal of Medicinal Chemistry). The compound shown below fits formula I with Ar = 3-pyridyl, W = a three carbon alkylene chain, Z = ethylene (-CH_2-CH_2-), T = nitrogen, U = V = CH, and m = n =0,. It has Registry Number 134266-18-5 and is found in Table I, page 114 of the reference. The compound is labeled **7**. Other compounds fitting formula I are **10**, **13**, and **16**. Biological testing of compound **7** is taught in the first complete paragraph on page 116. The DMSO solution described in line 8 is a composition. Thus, Applicant's claim 26 is anticipated.

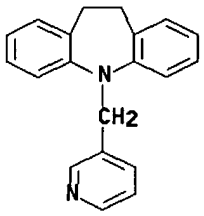


23. Claims 1, 3, 8, 9, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Ohshima (EP 549352 A2). There are seven compounds in this reference, which anticipate Applicant's claims. The compound shown below fits formula I with Ar = 5-tetrazolyl, W = methylene (-CH_2-), Z = ethylene (-CH_2-CH_2-), R^1 = methyl substituted by 2-ethyl-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-3-yl m = 1, and n =0,. It has Registry Number 150802-50-9 and is found in the figure on page 39 of the reference. It is compound 31. Other compounds fitting formula I are 32, 34-36, 39, and 40. See also claims 1-12, 17, and 18 of the reference.

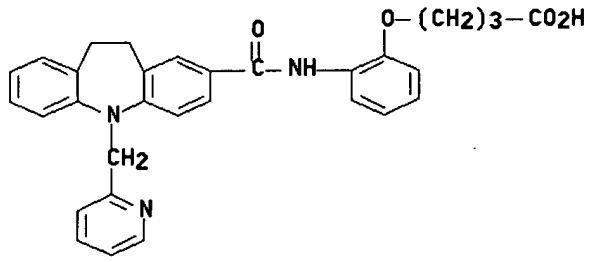


24. Claims 1, 3, 5, 8, 9, 11, 18, 19, and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Garforth (Journal of Enzyme Inhibition). There is one compound in this reference, which anticipate Applicant's claims. The compound shown below fits formula I with Ar = 3-pyridyl, V = nitrogen, W = methylene (-CH_2-), Z = ethylene (-CH_2-CH_2-), and m = n = 0. It has Registry Number 196392-53-7 and is found in Table I, page 167 of the reference. It is compound No. 18 and biological testing of compound 18 is taught in the last paragraph on page 163. The

solution described in lines 5-7 of the paragraph is a composition. Thus, Applicant's claim 26 is anticipated. Inhibition activity against the enzyme tyranothione reductase in taught in Table I. The expectation that compounds inhibiting this enzyme will be useful for treatment of Leishmania infections is taught in the paragraph spanning pages 162-163. Thus, Applicants claims 11, 18, and 19 are anticipated.



25. Claims 1, 3, and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Takami (JP 8-119920). There is one compound in this reference, which anticipate Applicant's claims. The compound shown below fits formula I with Ar = 2-pyridyl, U = nitrogen, T = V = CH, W = methylene (-CH_2-), Z = ethylene (-CH_2-CH_2-), and m = 1, n = 0, and R^1 = methyl substituted by oxo and with 2-amino-phenoxy-butanoic acid. It has Registry Number 179038-62-1 and is found in Table 1, page 6 of the reference. It is compound No. 20 and its' synthesis is found in lines 15-35, page 12.



26. Claims 1, 3, and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Beilstein (Ref AG). The compound of Accession number XP-002206576 fits formula I with Ar = phenyl, W = methylene, Z = vinyl (-CH=CH-), T = U = V = CH and m = n =0,. It has Registry Number 78943-58-5 and is pictured at the top of the page of the reference.

27. Claims 19-24 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolff (Burger's Medicinal Chemistry). In paragraphs 2-4, page 322 the reference teaches treatment of tuberculosis with streptomycin, isoniazid, p-aminosalicyclic acid, ethambutol, and rifampicin. None of these drugs is a sulfa drug and thus, Applicants' claim 22 is also anticipated. In the first complete paragraph on the right side of page 469, the references teaches treatment of *T. gondii* infections with a combination of pyrimethamine and sulfonamides. The reference to clinical results at the end of the first complete paragraph on page 323 makes clear that tuberculosis treatment is done in humans, which are mammals. Thus, claims 23 and 24 are anticipated.

28. Claims 19, 20, 22, 23, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by RM Corwin (University of Missouri College of Veterinary Medicine.). In paragraph 19 the reference teaches treatment of *T. gondii* infections

in cats with pyrimethamine or clindamycin. Thus, claim 25 is anticipated. Neither pyrimethamine nor clindamycin is a sulfa drug. Thus, claim 22 is anticipated.

Allowable Subject Matter

29. Claims 4, 6, and 7 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. Claim 10 would be allowable after deletion of the non-elected subject matter. The following is a statement of reasons for the indication of allowable subject matter: Applicants pteridine, purine, and the nitrogen-linked compounds of claim 4 are novel over the art cited above.

Conclusion

30. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Thomas McKenzie, Ph.D.
Patent Examiner
Art Unit 1624

TCMcK
February 26, 2003